UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,144	08/04/2003	Jin Lee	TRA-006.01	5095

25181 7590 10/29/2008

FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,144	LEE ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14 and 16-33* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,14,16-28,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-7-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 9-29-08 is acknowledged.

Claims included in the prosecution are 11, 13-14, 16-28 and 32-33.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 11, 13-14, 16-28 and 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to claim 11, the platinum compound is encapsulated and the encapsulation is either within sterols or phosphatidylcholine or a combination. It is unclear as to how one can encapsulate the compound within a Sterol since sterols by themselves have no bilayer or monolayer forming capability. Instant specification does not contain any examples showing the use of sterols alone.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 12, 16, 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abra cited above, in view of Ye et al (5,997,899).

Abra discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60-65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

What is lacking in Abra is the repetition of the heating and cooling. Abra does not teach the use of DPPC for the formation of liposomes

Ye et al while disclosing a method of preparation of liposomes teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

To employ three cooling and heating cycles in the method of preparation of liposomes of Abra would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC instead of HSPC taught by Abra would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Abra teaches liposome compositions containing lipids derivatized with a hydrophilic polymer for improved liposome stability and Ye describes a method of preparing multivesicular liposomal formulations having increased encapsulation efficiency by increasing the number of carbons in carbon chain at least one of the

amphiphilic lipids. Applicant argues that the Examiner has not provided "some articulated reasoning with some rational underpinning" for the skilled artisan to employ the temperature cycling of Ye in the process of Abra. In particular, there is no reason for the skilled artisan to employ Ye's temperature cycling, which was used with PC's having 14-20 carbons, in a formulation comprising the hydrophilic polymer modified liposomes of Abra, which are modified with, for example, PEG chains of 500-10,000 Daltons, with any reasonable expectation of success. According to applicant, nothing in the teachings of Ye suggest that temperature cycling would be facilitate drug equilibrium in a liposome comprising the hydrophilic polymer derived vesicles of Abra. Further according to applicant Ye only discloses the use of temperature cycling in a single example (Example 5) of the disclosure, which describes the preparation of multilamellar liposomes encapsulating cytarabine. As cytarabine is a small organic molecule, not a platinum compound, there is no reason the skilled artisan would readily conclude that platinum compounds would behave similarly to cytarabine and combine the teachings of Ye with Abra.

These arguments are not persuasive. First of all, Abra teaches liposomes having PEG and liposomes without PEG (Table 2). Second, instant claim language 'comprising' does not exclude PEG and furthermore, one would expect the drug loading to be the same irrespective of what lipids constitute the liposomes and applicant has not shown that to be otherwise. The examiner notes that applicants themselves claim sterols, phosphatidylcholines and a combination of these. Applicant is incorrect in stating that the examiner has not provided some articulated reasoning with some

rational underpinning for the skilled artisan to employ the temperature cycling of Ye, as required under KSR since according to Ye three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. This is clearly a rationale for one skilled in the art to employ three cycles. The motivation to combine need not be the same as applicants. With regard to applicant's arguments pertaining to Ye, the examiner points out that that Ye's teachings are for liposomes in general (example 5 in Ye is directed to multilamellar liposomes) and preferably multivesicular liposomes and instant claims do not exclude multivesicular liposomes. With regard to applicant's arguments pertaining to chain length in Ye, the examiner points out that in example 4 Ye teaches that the trend of increasing encapsulation efficiency with does not change. Applicant's argument that Ye only discloses encapsulating cytarabine which is a small molecule and not a platinum compound are not persuasive since Ye teaches the applicability of the method to a variety of biologically active compounds as evident from col. 5, line 30 through col. 6, line 19.

3. Claims 11, 13-14, 16-28 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi (US2002/0182248) in combination with Abra and Ye et al both cited above.

Yamauchi teaches a method of encapsulating a drug in liposomes by mixing the lipids with an aqueous solution of a drug, heating it above the transition temperature of the membrane and then cooling it. The preparation is extruded through a membrane filter (0043, 0051 and 0057). What is lacking in Yamauchi is the use of cisplatin as the drug and also repeating the steps of changing the temperature in two or more cycles.

Abra as pointed out above, discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60 to 65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

Ye et al as pointed out above, while disclosing a method of preparation of liposomes teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

The use of a platinum drug such as cisplatin in the method of Yamauchi would have been obvious to one of ordinary skill in the art since Yamauchi teaches that any drug can be encapsulated and the reference of Abra shows the knowledge in the art of encapsulating cisplatin. To employ three cooling and heating cycles in the method of preparation of liposomes of Yamauchi would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues the following:

> "Yamauchi describes "liposomes and liposomal dispersions in which stability of drugs which have poor stability in the aqueous solution is improved." *Yamauchi* at ¶ 7. In particular, Yamauchi states that the stability of the aforementioned drugs becomes "markedly excellent when they are incorporated in liposomes prepared

> using a specified lipid," where the sphingolipid is "the main component of the liposomal membrane." *Id.* at ¶ 8-9. Example 1 of Ye discloses the preparation of sphingolipid liposomes by adding an aqueous solution of PGE 1 to evaporated sphingomyelin and heating to 60 °C. *Id.* at ¶ 57.

These arguments are not persuasive. Although Yamaguchi teaches PGE in the examples, his teachings pertain to any drug. With regard to the specific lipid, sphingolipid in Yamaguchi as argued by applicant, The examiner points out that instant claim language of claim 11 does not exclude sphingomyelin. Furthermore, applicant has not provided any reasoning as to why liposome made with other phospholipids such as DPPC taught Yamaguchi would not behave the same way as the sphingomyelin containing liposomes. The examiner also points out that instant claim 11 recites generic phosphatidylcholine and Yamauchi teaches '1,2-dimyristoylamido-1,2-deoxyphosphatidylcholne in 0032 The examiner has already addressed applicant's arguments with regard to Ye and Abra.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK